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EXAMINER	
ROGERS, JAMES WILLIAM	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/668,045	CHAU ET AL.	
	Examiner	Art Unit	
	JAMES W. ROGERS	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6 and 9-56* is/are pending in the application.

4a) Of the above claim(s) *24-28,30-32,34-38 and 40-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-6 and 9-23,29,33,39,43-49,51-52 and 54-56* is/are rejected.

7)☒ Claim(s) *50 and 53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendments to the claims filed 07/07/2008 has been entered. Any rejection not addressed in the action below from the previous office action filed 03/05/2008 has been withdrawn.

Allowable Subject Matter

As recited in the previous office action filed 03/05/2008, claims 50 and 53 are objected to for depending upon rejected claims however their subject matter would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 1st and 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3,5-6 and 9-23,29,33,39,43-49,51-52 and 54-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons set forth in the previous office action filed 03/05/2008. A new rejection over the claims was also necessitated by applicants amendments to claims 1,12 and 13. Claims 1,12 and 13 all contain the new limitation that the polymeric carrier-conjugate is greater in size than **about** 6nm in size, however the specification at page 9 lines 12-19 states that the polymeric carrier in certain embodiments may be designed to

be greater than the renal excretion limit which is 6 nm, it never states **about** 6 nm, which is broader in scope than 6nm.

Claims 1-3,5-6 and 9-23,29,33,39,43-49,51-52 and 54-56 are rejected under 35 U.S.C. 112, first paragraph scope of enablement, for the reasons set forth in the previous office action filed 03/05/2008.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,12 and 13 all recite the limitation "polymeric carrier-conjugate". There is insufficient antecedent basis for this limitation in the claim.

Response to Arguments

Applicant's arguments filed 12/28/2007 have been fully considered but they are not persuasive.

Applicants assert that there is adequate written description within the specification and enablement for the limitations within claims 1-2 and 12-13. Applicants assert that the specification cites several references which disclose several list of known cleavage motifs as well as methods for determining cleavage motifs for digestive enzymes, such as substrate phase display libraries, position scanning peptide libraries and mixture-based peptide libraries. Applicants assert these references provide reasonable amount of guidance for determining the recognition sequences in the claimed conjugates and these methods would be routine to one of ordinary skill in the art. Thus applicants surmise one skilled in the art would have no difficulty in determining

additional sequences that can be cleaved by the enzymes specified within claim 1 and this would be undue experimentation. Applicants state they have clearly shown how one of ordinary skill in the art can determine the cleavage motif of a target enzyme **when it is not yet known**, determine peptide substrates for known enzymes and identify sequences which are labile to a target enzyme. Applicants also assert that the methodology used to prepare the conjugates of the examples can be used with other peptide linkers since peptides generally contain the same or similar functional groups. Thus applicants surmise the examiner has provided no evidence that the methods of synthesis and/or assays described in the examples cannot be used with other peptide linkers. Applicants assert that the examiner is silent and provides no evidence in regards to how the references and assays described are undue experimentation.

Regarding the written description rejection, the relevance of the above assertions is unclear. It appears as though the entirety of applicant's arguments is based on an **invitation to experiment** using technology in methods for determining cleavage motifs for digestive enzymes. An invitation to experiment is insufficient in regards to written description, the specification must reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have not shown that they had possession of any peptide sequences other than IPVGLIG which is cleavable by MMP-2. Applicants seem to be relying on the argument that it would have been obvious to one of ordinary skill in the art to use the methodologies described in the prior art cited within applicants specification to determine cleavage motifs for digestive enzymes. A description that does not render

a claimed invention obvious does not sufficiently describe that invention. But a description that renders obvious a claimed invention does not necessarily satisfy the written description requirement. Eli Lilly, 119 F.3d at 1567, 43 USPQ2d at 1405. Also see In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) ("If n-propylamine had been used in making the compound instead of n-butylamine, the compound of claim 13 would have resulted. Appellants submit to us, as they did to the board, an imaginary specific example patterned on specific example 6 by which the above butyl compound is made so that we can see what a simple change would have resulted in a specific supporting disclosure being present in the present specification. The trouble is that there is no such disclosure, easy though it is to imagine it.") (emphasis in original). It is the position of the examiner that applicants have not described their invention in a detailed enough manner to give support for their broadly disclosed invention within claims 1,12 and 13. Applicants have only described a narrow subset of peptide sequences that are known to be cleaved by digestive enzymes, even if the sequences of the Turk are included in the written support. The number of species described is insufficient to provide support for the very broad genus of **any** peptide cleavable by a serine protease or matrix metalloproteinase. There is essentially no nexus between what is described and what is claimed and there is no reason to believe that someone skilled in the art would have immediately envisioned applicants claimed invention. Applicants have essentially only given an incomplete plan on how the peptide sequences may be found and synthesized. The plan is incomplete because applicants have only described vague information or general ideas that may or may not

be workable in order to find a digestive enzyme that is overexpressed in a diseased tissue (the enzyme as applicant's state may not even be known) and then developing a sequence that is cleaved by that specific enzyme.

Regarding the enablement rejection as in the above written description remarks by the examiner the relevance of applicant's assertions is unclear. As already stated above applicants appear to be relying on the argument of an **invitation to experiment** using technology in methods for determining cleavage motifs for digestive enzymes and it would be obvious to the skilled artisan to conduct such experiments/assays. This argument is not persuasive in view of the enablement rejection above. Applicants are essentially stating that an assay to find what peptides are cleavable by a very broad genus of digestive enzymes is not undue experimentation. The examiner disagrees because as stated in the rejection above the fact that an assay must be performed to find the right peptide sequence supports the examiners view that predictability in discovering peptides that are cleavable by specific digestive enzymes is low because the enzyme is very selective. Thus an assay must be performed so that the peptides that are cleavable by a specific enzyme can be found. The time to experiment and discover the small subset of sequences that have the desired structural characteristics would be undue for one skilled in the art. Applicants' assertion that the methodology of the examples can be used to make other peptides is also found unpersuasive. The examiner has clearly shown that discovering peptides that are cleavable by the specific digestive enzymes claimed is unpredictable. Therefore the lack of working examples

outside of the peptide linker IPVGLIG, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2194.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3,5-6,9-13,17,21,29,33,39,43,47,51-52 and 54-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Copland et al. (WO 01/68145 A2), for the reasons set forth in the previous office action filed 03/05/2008.

Applicant's arguments filed 07/07/2008 have been fully considered but they are not persuasive.

Applicants assert that Copeland cannot anticipate their new limitation that the polymeric carrier-conjugate is greater than about 6 nm is size, because the PEG capping group only has 2-10 monomer units.

The relevance of this assertion is unclear. It is noted by the examiner that applicant's new limitation is referring to the entire carrier-conjugate, not just the polymeric carrier. Applicants have provided no evidence that the doxorubicin-peptide conjugates would be smaller than 6 nm. Indeed as mentioned in previous office action the remaining portion of the peptide sequence not cleaved by the digestive enzyme can also be considered as a polymeric carrier.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3,5-6,9-14,17,18,21,22,29,33,39, 43,44,47-48,51-52 and 54-56 are rejected under 35 U.S.C. 102(b) as being unpatentable by Duncan et al. (WO 98/56425, cited in last office action) in view of Copeland et al. (WO 01/68145 A2).

Applicant's arguments filed 07/07/2008 have been fully considered but they are not persuasive.

Applicants assert that a combination of Copeland and Duncan is impermissible because Duncan teaches away from administering a conjugate containing a linker that is cleaved by a digestive enzyme overexpressed by the tissue itself since Duncan must administer the enzyme sequentially.

Firstly the examiner notes that independent claim 1 does recite that the digestive enzyme is overexpressed by the tissue, however the claim is clearly drawn to a conjugate, in other words a compound. Since the combination of Duncan and Copeland disclose conjugates that are within the scope of applicants claimed invention the claims are prima-fascia obvious, because the same compound will inherently have the same properties and will be capable of being cleaved by the same enzymes if the structures are the same. Secondly the other independent claim 13 does not even recite that the digestive enzyme is overexpressed by a tissue. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Clearly the examiner noted that Duncan does not mention that tissues overexpress the digestive enzyme which is why it was combined with Copeland who does disclose that amino acid recognition sequences are used in targeted cancer treatments wherein the enzyme is inherently overexpressed in the cancerous tissue. The motivation for combining them would be to produce an advantageous drug conjugate comprising a chemotherapeutic drug such as doxorubicin or methotrexate linked to a polymeric carrier such as dextran through an oligopeotide linker cleavable by MMP-2. One with skill in the art would have had a reasonable expectation of success in substituting/modifying the peptide sequences of Copeland with the linkers Duncan because the linkers are related in that they are used to target tissue and are cleavable by digestive enzymes thus the peptides are related in their use and function. The advantage of modifying the linkers of Duncan with the MMP-2 cleavable peptides within Copland would be that the that the prodrug would be targeted to tissue where MMp-2 is over expressed such as carcinomas tissue, thus the compounds are inactive or significantly less active upon administration to non-diseased tissue, thus lowering the toxicity.

Applicants further assert as in their arguments summarized above that Copeland the PEG oligomers taught are too small too read on the newly amended claims.

As discussed above applicant's claims limit the entire conjugate not just the polymeric carrier; furthermore the polypeptides of Copeland can also read on polymeric carrier.

Applicants lastly assert that their invention includes results that are unexpected in view of Duncan that requires co-administration of the enzyme with the conjugate. Applicant's state the examples show that the presence of a peptide linker containing a recognition segment promotes cleavage of the conjugate in the extracellular space of the tumor tissue where the digestive enzyme is overexpressed. Applicants also assert that dextran-methotrexate was significantly more toxic than dextran-oligopeptide-methotrexate.

The relevance of these assertions is unclear. Firstly Duncan discloses prodrugs that contain a drug connected to a peptide linker that is further connected to a hydrophilic polymer, Duncan does not disclose a pro-drug consisting of only a drug and a carrier such as dextran-methotrexate. Secondly as described above claim 1 is drawn to a conjugate or a compound thus if the prior art discloses the same compound it will still read on applicants claims. Thirdly as noted above claim 13 does not include a limitation that the enzyme is overexpressed by the tissue itself. The examiner noted in the last office action that Duncan is silent on tissues overexpressing the digestive enzyme; however Copeland does disclose that amino acid recognition sequences are used in targeted cancer treatments wherein the enzyme is inherently overexpressed in the cancerous tissue. Thus when the knowledge of prior art is considered as a whole it was already well known that cancerous tissue overexpresses certain enzymes such as MMp-2, and these enzymes could be targeted using known recognition segments. Thus there is hardly anything unexpected by applicants claimed invention in that it was already well known that amino-acid recognition segments could be targeted to

cancerous tissue which overexpresses the digestive enzymes that cleave those sequences.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James W. Rogers, Ph.D. whose telephone number is (571) 272-7838. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618